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(54) Nucleosides of 5-monofluoromethyluracil and 5-difluoromethyluracil.

(57) A method for synthesizing monofluoromethyl- and difluoromethyluracil nucleosides from the corresponding thymine nucleosides is developed. These compounds which contain a partially fluorinated methyl group at the C-5 position (a new class of nucleosides) are potential antiviral and/or anti-cancer agents. The major features of the preparative route involve bromination of suitably protected thymine nucleosides followed by fluoride treatment.

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10 Nucleosides of 5-Monofluoromethyluracil and
 5-Difluoromethyluracil

15 The invention described herein was made in the course of
 work under a grant from the U.S. Department of Health and
 Human Services.

BACKGROUN

20 5-Trifluoromethyluracil was originally synthesized in
 very low yield by a multistep procedure starting from
 trifluoroacetone-cyanohydrin (Heidelberger, et al., J.
 Am. Chem. Soc., 84, 3527 (1962); J. Med. Chem. 1, 1
 (1964)). Later, this compound was prepared more con-
25 veniently from uracil-5-carboxylic acid by treatment
 with sulfur tetrafluoride (Mertes, et al., J. Med.
 Chem., 9, 876 (1964)). The 2'-deoxynucleoside, i.e., 1-
 (2'-deoxy- β -D-erythropentofuranosyl)-5-trifluoromethyl-
 uracil or F TDR, was prepared by condensation of the
30 base and sugar halide in very low yield. (Heidelberger,
 Progr. Nucleic Acid Res. Mol. Biol., 4, 1 (1965); Cancer
 Res., 30, 1549 (1970)).

35 5-Difluoromethyluracil was also prepared but was found
 to be extremely labile in neutral aqueous media (Mertes,
 et al., loc. cit). No nucleosid containing this base has
 been synthesized. Attempts to synthesize 5-monofluoro-

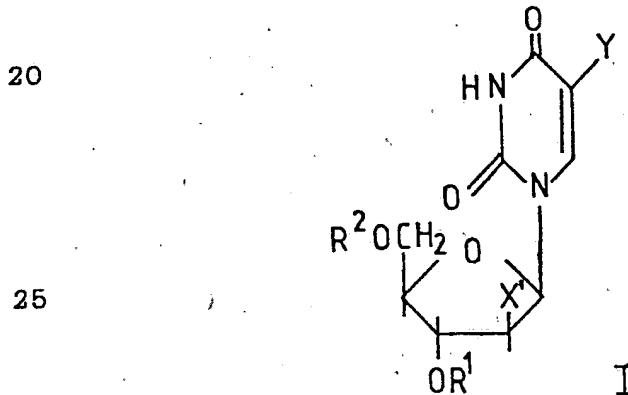
1 uracil have failed (Mertes, loc. cit). No 5-monofluoro-
 5 methyluracil nucleoside is known.

Our theoretical considerations suggest that substitution
 5 of the N-1 position of 5-(partially-fluorinated)-methyl-
 uracils with an alkyl or sugar moiety should decrease
 the lability of the fluorine in the heterocyclic base.
 Therefore, nucleosides containing 5-(partially fluorinated)
 10 methyluracils should be obtainable by synthesis
 from a preformed nucleoside.

SUMMARY

15 Nucleosides of the invention can be represented by
 Formula I as follows:

Formula I



30 Wherein either X or X' is always H.
 X or X' is H, OR³, or a halogen such as fluorine,
 chlorine, bromine or iodine as well as pseudohalogen
 such as lower alkylsulfonyl group of 1 to 5 carbons such
 as methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobu-
 35 tyl-, sec-butyl-, tert-butyl, and pentylsulfonyl or
 arylsulfonyl such as benzene-, p-toluene-, p-nitro-
 benzenesulfonyl grouping.

1 Y is monofluoromethyl (CH_2F) or difluoromethyl (CHF_2).
 R₁, R₂ and R₃ are the same or different and are hydrogen or aryl groups of 1 to 20 carbon atoms such as formyl, acetyl, propionyl, isopropionyl, butyryl, isobutyryl,
 5 tert-butyryl, valeryl, pivaloyl, caproyl, capryl, lauryl, myristyl, palmityl, stearyl, arachidyl, stiglyl, palmitoyl, oleyl, linolenyl, arachidonyl and the like, or trisubstituted silyl groups such as tert-butyldimethylsilyl, tert-butyldiphenylsilyl, dimethylphenylsilyl and the like.

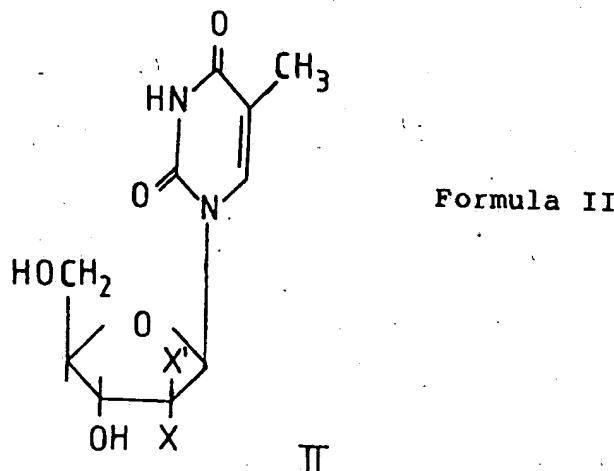
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DESCRIPTION OF INVENTION

15 The present invention relates to the novel class of nucleosides which contain 5-monofluoromethyluracil or 5-difluoromethyluracil as their aglycon. A further aspect of the present invention relates to processes for preparing uracil nucleosides containing a partially fluorinated methyl group at the C-5 position and intermediates useful therein.

20

The starting materials for the process of the present invention can be subsumed under general Formula II, as follows:



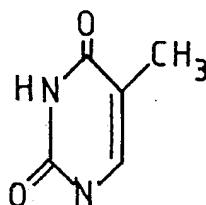
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X or X¹ is hydrogen
 X or X¹ is as defined previously.

1 Nucleosides of Formula II are acylated with alkanoic acid chloride or alkanoic acid chloride or alkanoic acid anhydride in organic base such as pyridine or triethylamine. Acylation of Formula II nucleosides is also achieved with alkanoic acid chloride or alkanoic acid anhydride in aprotic solvent such as methylene chloride, chloroform, dichloroethane or tetrachloroethane in the presence of organic base such as pyridine, lutidine, collidine, triethylamine, N,N-diethylaniline, p-(dimethylamine)pyridine, 1,8-diazabicyclo(5,4,0)undec-7-ene or 1,5-diazabicyclo(4,3,0)-non-5-ene.

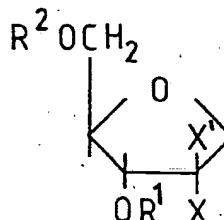
Upon completion of the reaction, the reaction mixture is quenched suitably, by adding excess alkanol such as 15 methanol, ethanol, propanol and the like, to hydrolyze the acylating reagent. After concentration of the mixture, the acylated intermediates can be obtained in pure condition either by direct crystallization of the residue from various solvents or solvent systems, or by 20 chromatography over a column of silica gel G60 using various solvent systems. The acylated intermediates

25



Formula III

30



III

obtained by the above procedure can be presented under 35 general Formula III, wherein
 X or X_1^1 is always hydrogen
 X or X_1^1 or X_3^3 is OR_1 , or a halogen such as fluorine, chlorine,

1 bromine or iodine as well as pseudohalogen such as lower alkylsulfonyl group of 1 to 5 carbons such as methyl-, ethyl-, propyl-, isopropyl, butyl-, isobutyl-, sec-butyl, tert-butyl- and pentylsulfonyl or arylsulfonyl
 5 such as benzene-, p-toluene-, p-nitrobenzenesulfonyl grouping.

1, 2 and 3 R, R and R are the same and are aryl groups of 1 to 20 carbon atoms such as formyl, acetyl, propionyl, iso-
 10 propionyl, butyryl, isobutyryl, tert-butyryl, valeryl, pivaloyl, caproyl, capryl, lauryl, myristyl, palmityl, stearyl, arachidyl, stilligyl, palmitoyl, oleyl, linolenyl, arachidonyl and the like.

15 Nucleosides of Formula II are also converted into the corresponding partially silylated intermediates by treatment with trisubstituted-silyl chloride such as tert-butyldimethylsilyl, tert-butyldiphenylsilyl or dimethylphenylsilyl chloride in organic base such as
 20 pyridine or triethylamine. Silylation of Formula II nucleosides can also be performed with trisubstituted-silyl chloride in aprotic solvent such as methylene chloride, chloroform, dichloroethane, tetrahydrofuran, dioxan, benzene, acetonitrile, ethyl acetate and the
 25 like in the presence of organic base such as pyridine, lutidine, collidine, triethylamine, N,N-diethylaniline, p-(dimethylamino)pyridine, 1,8-diazabicyclo(5,4,0)undec-7-ene or 1,5-diazabicyclo(4,3,0)non-5-ene. The silylation reaction is carried out at -40° to 174°C (preferably
 30 from 20° to 30° C), in a period of from 1 hour to 6 days.

When the reaction is carried out without solvent, or in a water-missible aprotic solvent, the mixture is concentrated in vacuo, the residue dissolved in an aprotic solvent such as methylene chloride, chloroform, benzene or the like, and washed with water, dried over sodium sulfat or magnesium sulfate and then concentrated in

1 vacuo. After the reaction is performed in an aprotic solvent not miscible with water, the mixture is added into cold water, the organic layer separated, dried over sodium sulfate or magnesium sulfate, and then concentrated in vacuo. The residue is purified either by direct crystallization or by chromatography on a silica gel G60 column using various solvent systems.

10 The silylated intermediates can be subsumed under general Formula III wherein:
X or X^1 is hydrogen.
X or X^1 is OR^3 , a halogen such as fluorine, chlorine, bromine or iodine as well as a pseudohalogen such as the lower alkylsulfonyl group of 1 to 5 carbons such as
15 methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobutyl-, sec-butyl-, tert-butyl and pentylsulfonyl or arylsulfonyl such as benzene-, p-toluene-, p-nitrobenzenesulfonyl grouping.

20 Among R^1 , R^2 and R^3 , one or two are trisubstituted-silyl groups such as tert-butyldimethyl-, tert-butyldiphenyl- or phenyldimethylsilyl groupings, and the rest are hydrogen.

25 The intermediates of Formula III nucleosides are reacted with 1 or 2 equivalents of bromine under ultraviolet light irradiation in polyhalogenated carbon solvent such as carbon tetrachloride at a temperature range of from 0° to 77° C in a period of from 1 to 6 hours. When 1
30 equivalent of bromine is used, 5-monobromomethyluracil nucleosides (Formula I, Y = CH_2Br) are formed. Reaction of Formula III intermediates with 2 equivalents of bromine results in the formation of 5-dibromomethyluracil nucleosides (Formula I, Y = $CHBr_2$).

35 Upon completion of the reaction, nitrogen gas is bubbled through the mixture for a period of from 10 minutes to 1

1 hour (preferably 30 minutes), to remove hydrogen bromide which is produced during the bromination reaction. The mixture is then concentrated in vacuo to afford crude bromomethyluracil intermediates (Formula I, Y = CH_2Br or CH_2Br_2) which can be purified as a very unstable powder. More practically, the mixture can be fluorinated directly without purification of the bromomethyl-uracil intermediates. Thus, the crude intermediates are dissolved in an appropriate, aprotic solvent and a fluorinating agent is added. When silver fluoride is used as a fluorinating agent, acetonitrile is the preferred solvent. When tetrabutylammonium fluoride is employed as the fluorinating agent tetra-hydrofuran is the more suitable solvent. Acetone is recommended when Amberlyst A-26 (F⁻) is used as the fluorinating agent.

The mixture is stirred vigorously at a temperature range of from -40° to 80° C (preferably from -10° to 30° C), for a period of from 5 minutes to 5 hours. The mixture is filtered from insoluble materials and the filtrate is washed with water, dried over sodium sulfate or magnesium sulfate, concentrated in vacuo, and the residue chromatographed over a column of silica gel G60 using various solvent systems, preferably n-hexane-ethyl acetate or a methylene chloride-tetrahydrofuran combination.

The free Formula I nucleosides wherein Y is CH_2F or CH_2F_2 and R¹ and R² are hydrogen, is prepared from the corresponding acyl intermediates (Formula III, wherein Y is CH_2F or CH_2F_2 , R¹ and R² are the same and alkonyl groups) by treatment with mineral acid in water or alkanol, preferably 1 % to 5 % hydrogen chloride in methanol. More preferably, the free nucleosides of Formula I are prepared from the corresponding partially silylated intermediates (Formula III, Y is CH_2F or CH_2F_2 , R¹ and/or R² is/are trisubstituted silyl and X¹ or X² is OH or

- 1 trisubstituted silyloxy group) by treatment with fluoride ion in an appropriate solvent, preferably with tetra-n-butylammonium fluoride in tetrahydrofuran.
- 5 The free nucleosides (Formula I, Y is CH_2F or CHF_2 , R^1 and R^2 are hydrogen) and their acylated analogs (Formula I, Y is CH_2F or CHF_2 , R^1 and R^2 are the same or different and alkanoyl) may be useful therapeutic agents exhibiting antiviral and/or anticancer activity, and may
- 10 be employed in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier which can be an organic or inorganic inert carrier material suitable for enteral or parenteral administration such as, for example, water,
- 15 gelatin, gum arabic, lactose, starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, petroleum jelly, etc. The pharmaceutical preparations can be made up in solid form (e.g., as tablets, dragees, suppositories or capsules), or in liquid form (e.g., as
- 20 solutions, suspensions or emulsions). The preparations may be sterilized and/or may contain adjuvants such as preserving, stabilizing, wetting or emulsifying agents, salts for varying the osmotic pressure, or buffers. Such preparations may also contain other therapeutic agents.

25 The following examples are illustrative of the process and products of the present invention, but are not to be construed as limiting.

30

EXAMPLE 1

1-(2-Deoxy-2-fluoro- β -D-arabinofuranosyl)thymine (1.5 g, 5.76 mmol) is dissolved in dry pyridine (15 ml) and 35 acetic anhydride (5 ml) is added. The mixture is stirred overnight at room temperature and is then concentrated in vacuo. The residue is chromatographed on a column of

1 silica gel G60 using n-hexano-ethyl acetate (1:2) as the
 5 eluent. Upon evaporation of the major UV-absorbing frac-
 10 tion, 1-(3, 5-di-O-acetyl-2-deoxy-2-fluoro- β -D-arabino-
 15 furanosyl)thymine (1.62 g, 82 %) is obtained as a
 20 colorless amorphous solid.

1 ^1H NMR (CDCl_3) 1.94 (3H, s, Me), 2.13 (3H, s, Ac),
 5 2.17 (3H, s, Ac), 4.25 (1H, m, H-4'), 4.44 (2H, m, H-
 10 5'5"), 5.10 (1H, dd, H-2', $J_{2',F} = 49.95$, $J_{1',2'} = 2.74$
 15 Hz), 5.23 (1H, dd, H-3', $J_{3',F} = 16.88$, $J_{1',3'} = 2.61$),
 20 6.22 (1H, dd, H-1', $J_{1',F} = 21.95$, $J_{2',3'} = 2.74$), 7.33
 25 (1H, s, H-6), 9.91 (1H, s, NH, exchangeable).

1 Microanalysis ($\text{C}_{14}\text{H}_{17}\text{FN}_2\text{O}_7$). Calcd: C, 48.84; H, 4.98; N,
 5 8.14. Found: C, 48.98; H, 5.12; N, 8.08.

1 By following the same procedure but using the correspon-
 5 ding 2'-substituted nucleosides as starting materials,
 10 the following compounds are also prepared:

15 1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy- β -D-
 20 arabinofuranosyl)thymine.
 25 1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy- β -D-
 30 arabinofuranosyl)thymine.
 35 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-iodo- β -D-
 40 ribofuranosyl)thymine.
 45 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro- β -D-
 50 ribofuranosyl)thymine.
 55 1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy- β -D-
 60 ribofuranosyl)thymine.
 65 1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy- β -D-
 70 ribofuranosyl)thymine.
 75 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-iodo- β -D-
 80 ribofuranosyl)thymine.

1 EXAMPLE 2

A mixture of thymidine (0.50 g, 2.06 mmol) and tert-butyldiphenylsilyl chloride (0.60 ml, 2.31 mmol) in dry 5 pyridine (10 ml) is stirred overnight at room temperature, and then concentrated in vacuo. The residue is dissolved in methylene chloride and the solution washed with water, dried over sodium sulfate and concentrated in vacuo. The residue is crystallized from acetone-n-10 hexane to afford S'-0-tert-butyldiphenylsilylthymidine (600 mg), mp 170-171°C. An additional amount (150 mg) of the silylated product is obtained from the mother liquor, giving a total yield of 76 %. ^1H MNR (CDCl_3) 1.09 (9H, s, t-Bu), 1.64 (3H, s, Me), 1.94-2.63 (2H, m, 15 H-2',2''), 3.70-4.12 (3H, m, H-4',5',5''), 4.57 (1H, m H-3'), 6.41 (1H, dd, H-1', J_{1',2'} = 7.93, J_{1',2''} = 6.10 Hz), 7.26-7.76 (11H, m, H-6 and Ph), 8.94 (1H, s, NH, exchangeable).

20 Microanalysis ($\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_5\text{Si}$). Calcd: C, 64.97; H, 6.71; N, 5.83. Found: C, 65.05; H, 6.75; N, 5.91.

By following the same procedure but using the corresponding 2'-substituted nucleoside analogs as starting materials, the following compounds are also prepared:

- 1-(5'-0-tert-Butyldiphenylsilyl-2-deoxy-2-fluoro- β -D-arabinofuranosyl)thymine.
- 1-(5'-0-tert-Butyldiphenylsilyl-2-chloro-2-deoxy- β -D-arabinofuranosyl)thymine.
- 1-(5'-0-tert-Butyldiphenylsilyl-2-bromo-2-deoxy- β -D-arabinofuranosyl)thymine.
- 1-(5'-0-tert-Butyldiphenylsilyl-2-deoxy-2-fluoro- β -D-ribofuranosyl)thymine.
- 1-(5'-0-tert-Butyldiphenylsilyl-2-chloro-2-deoxy- β -D-ribofuranosyl)thymine.

1 1-(5'-0-tert-Butyldiphenylsilyl-2-bromo-2-deoxy-β-D-ribofuranosyl)thymine.

5 EXAMPLE 3.

To a solution of 5-methyluridine (3.00 g, 10.06 mmol) and tert-butyldiphenylsilyl chloride (6.50 ml, 25.0 mmol) in dry N,N-dimethylformamide (60 ml) is added 10 imidazole (3.00 g, 44.07 mmol), and the mixture is stirred overnight at room temperature. The solvent is removed in vacuo and the residue is partitioned between methylene chloride and water. The organic layer is separated, washed twice with water and concentrated in 15 vacuo. The residue is chromatographed over a column of silica gel G60 using carbon tetrachloride-acetone (10:1) as the eluent. Two fractions are obtained. Upon evaporation of the first fraction in vacuo and crystallization of the residue from carbon tetrachloride-petroleum 20 ether, 1-(2',5'-di-0-tert-butyldiphenyl-β-D-ribofuranosyl)thymine (3.78 g, 51 %) is obtained, mp 97-99 °C.

¹H NMR (CDCl₃) 0.92 (9H, s, t-Bu), 1.11 (9H, s, t-Bu), 1.58 (3H, d, 5-Me, J_{Me,6} = 1.24 Hz), 3.73 (1H, dd, H-5', J_{5',5"} = 11.73, J_{4',5"} = 1.64), 3.91 (1H, dd, H-5", J_{5',5"} = 11.73, J_{4',5"} = 1.92), 4.18 (1H, m, H-4'), 4.39 (2H, m, H-2',3'), 6.20 (1H, m, H-1'), 6.78 (1H, d, H-6, J_{Me,6} = 1.24), 7.10-7.71 (20H, m, Ph), 7.81 (1H, broad s, NH, exchangeable).

30 Microanalysis (C₄₂H₅₀N₂O₂Si₂.2H₂O) Calcd: C, 65.21; H, 7.06; N, 3.63. Found: C, 65.20; H, 7.10; N, 3.44.

From the second fraction, 1-(3',5'-di-0-tert-butyldiphenylsilyl-β-D-ribofuranosyl)thymine (1.86 g, 25 %) is 35 obtained, after recrystallization from benzene-hexane, mp 86-89 °C. ¹H NMR (CDCl₃) 0.96 (9H, s, t-Bu), 1.13 (9H, s, t-Bu), 1.49 (3H, s, 5-Me), 2.81 (1H, dd, H-5',

1 $J_{5',5''} = 11.66$, $J_{4',5'} = 1.92$, 3.54 (1H, dd, H-5''),
 $J_{5',5''} = 11.66$, $J_{4',5''} = 1.88$, 3.77 (1H, m, H-4'),
4.19 (1H, m, H-3'), 4.46 (1H, m, H-2'), 6.16 (1H, d, H-
1', $J_{1',2'} = 7.68$), 7.08-7.78 (21H, m, H-6 and Ph), 8.35
5 (1H, s, NH, exchangeable).

Microanalysis (C₄₂H₅₀N₂O₆Si₂) Calcd: C, 68.63; H, 6.80;
N, 3.81. Found: C, 68.74; H, 7.09; N, 3.65.

10 By following the same procedure but using 1-(β -D-arabinofuranosyl)thymine as the starting material, 1-(3',5'-di-O-tert-butyldiphenylsilyl- β -D-arabinofuranosyl)thymine and 1-(2,5-di-O-tert-butyldiphenylsilyl- β -D-arabinofuranosyl)thymine are also prepared.

15

EXAMPLE 4

A mixture of 3',5'-di-O-acetylthymidine (4.50 g, 13.78
20 mmol) in carbon tetrachloride (900 ml) is refluxed under
nitrogen until a clear solution is obtained. A solution
of bromine (0.8 ml, 15.61 mmol) in carbon tetrachloride
(18 ml) is very slowly added to the refluxing solution
over a period of 2 to 3 hours, while the reaction mix-
25 ture is irradiated with a 500 watt UV lamp. After all
the bromine is added, nitrogen is bubbled through the
solution for 30 minutes to remove hydrogen bromide. The
solution is concentrated to dryness in vacuo. The crude
5-bromomethyl-uracil nucleoside intermediate thus ob-
30 tained is dissolved in anhydrous acetonitrile (50 ml)
and treated with powdered silver fluoride (8 g, 63.10
mmol) for 15 minutes with vigorous stirring at room
temperature. The precipitate is removed by filtration
and the filtrate is concentrated to dryness in vacuo.
35 The residue is dissolved in chloroform, washed successi-
vely with water and saline, dried over sodium sulfate
and concentrated to dryness. The residue is chromatogra-

1 phed on a column of silica gel G60 using n-hexane-ethyl acetate (1:1). Upon evaporation of the major fraction in vacuo and crystallization of the residue from methylene chloride-ether-petroleum ether, 1-(3',5'-di-O-acetyl- β -D-*erythropentofuranosyl*)-5-monofluoromethyluracil (1.5 g, 32 %) is obtained, mp 24-27° C. 1 H NMR ($CDCl_3$) & 2.12 (6H, s, 3',5'-Ac), 2.24 (1H, m, H-2'), 2.57 (1H, dq, H-2", $J_{2',2''} = 14.27$, $J_{1',2''} = 5.77$, $J_{2'',3'} = 2.06$), 4.31 (3H, m, H-4',5',5''), 5.19 (2H, dd, ^{CH_2}F , $J_{H,F} = 47.48$, $J_{H,H} = 3.29$), 5.25 (1H, m, H-3'), 6.32 (1H, dd, H-1', $J_{1',2'} = 8.24$, $J_{1',2''} = 5.77$), 7.69 (1H, d, H-6, $J_{6,F} = 2.47$).

Microanalysis (C₁₄H₁₇FN₂O₇) Calcd: C, 48.84; H, 4.98; F, 5.52; N, 8.14. Found: C, 49.14; H, 5.21; F, 5.21; N, 7.87.

EXAMPLE 5

1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro- β -D-arabinofuranosyl)thymine (170 mg, 0.49 mmol) is brominated by a procedure described in Example 4. The crude 5-bromo-methyluracil nucleoside is dissolved in anhydrous tetrahydrofuran (1 ml) and 0.5 M tetra-n-butylammonium fluoride in tetrahydrofuran (2 ml) is added. The mixture is stirred for 30 minutes at room temperature and then chromatographed on a silica gel G60 column using n-hexane-ethyl acetate (1:2) as the eluent. 1-(3,5-Di-O-acetyl-2-deoxy-2-fluoro- β -D-arabinofuranosyl)-5-Mono-fluoromethyluracil (22 mg, 12 %) is obtained after concentration of the nucleoside-containing fraction and crystallization of the residue from benzene; mp 109-110° C. 1 H NMR ($CDCl_3$) & 2.12 (3H, s, Ac), 2.17 (3H, s, Ac), 4.26 (1H, m, H-4'), 4.46 (2H, m, H-5',5''), 5.13 (1H, dd, H-2', $J_{2',2''} = 50.22$, $J_{1',2'} = 2.74$ Hz), 5.18 (2H, d, ^{CH_2}F , $J_{H,F} = 47.74$), 5.24 (1H, dd, H-3', $J_{3',F} = 16.60$,

1 $J_{2',3'} = 2.06$, 6.22 (1H, dd, H-1', $J_{1',F} = 21.40$,
 $J_{1',2'} = 2.74$), 7.73 (1H, broad s, H-6'), 9.36 (1H, broad
s, NH, exchangeable).

5 Microanalysis (C₁₄H₁₆F₂N₂O₇) Calcd: C, 46.41; H, 4.45;
F, 10.49; N, 7.73. Found: C, 46.15; H, 4.51; F, 10.31;
N, 7.75.

10 EXAMPLE 6

Crude 1-(5'-O-tert-butyldiphenylsilyl-2'-deoxy- β -D-
erythropentofuranosyl)-5-monobromouracil (obtained by
bromination of 5-O-tert-butyldiphenylsilylthymidine (120
15 mg, 0.25 mmol) is dissolved in dry acetone (5 ml) and
amberlyst A-26 (F₂) (0.5 g) is added. The mixture is
vigorously stirred at room temperature four 1 hour and
the resin is filtered and washed with acetone. The
concentrated filtrate and washings are concentrated in
20 vacuo and the residue chromatographed over a column of
silica gel G60 using n-hexane-ethyl acetate (1:3). 1-
(5'-O-tert-Butyldiphenylsilyl-2'-deoxy- β -D-erythropento-
furanosyl)-5-monofluorouracil (26 mg, 21 %) is obtained
in pure form after crystallization from n-hexane-
25 methylene chloride, mp 129-131 C. ¹H NMR (CDCl₃) & 1.04
(3H, s, Me in tBu), 1.08 (6H, s, 2Me in tBu), 1.96-2.62
(2H, m, H-2',2''), 3.75-4.19 (3H, m, H-4',5',5''), 4.80
(2H, d, CH₂F, $J_{2',F} = 47.92$ Hz), 6.22 (1H, dd, H-1',
 $J_{1',2'} = 5.76$, $J_{1',2''} = 7.41$), 7.29-7.77 (10H, m, Ph),
30 7.83 (1H, d, H-6', $J_{6',F} = 3.35$), 8.45 (1H, broad s, NH,
exchangeable).

Microanalysis (C₂₆H₂₁FN₂O₅Si) Calcd: C, 62.63; H, 6.27;
F, 3.81; N, 5.62. Found: C, 62.66; H, 6.36; F, 3.66; N,
35 5.78.

1 The following 5-monofluoromethyluracil nucleosides are prepared by following the same procedures described in Example 4 and Example 6 but using the corresponding blocked nucleoside intermediates. When the silver fluoride-acetone combination as in Example 4 is used, the yields are 30% - 55%, whereas the Amberlyst A-26 (F⁻)-acetone procedure as in Example 6 gives the following products in 20% - 40% yields:

- 10 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-monofluoromethyluracil
- 15 1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil
- 20 1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil
- 25 1-(5'-0-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-monofluoromethyluracil.
- 30 1-(5'-0-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil.
- 35 1-(2',3',5'-Tri-O-acetyl-β-D-arabinofuranosyl)-5-monofluoromethyluracil
- 40 1-(2',5'-Di-O-tert-butyldiphenylsilyl-β-D-arabinofuranosyl)-5-monofluoromethyluracil
- 45 1-(3',5'-Di-O-tert-butyldiphenylsilyl-β-D-arabinofuranosyl)-monofluoromethyluracil
- 50 3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-5-monofluoromethyluridine
- 55 3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-5-monofluoromethyluridine
- 60 3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-5'-0-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-5-monofluoromethyluridine.
- 65 3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5-monofluoromethyluridine.

1. 5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5-monofluoromethyluridine.
2. 2',3',5'-Tri-0-acetyl-5-monofluoromethyluridine
3. 2',5'-Di-0-tert-butyldiphenylsilyl-5-monofluoromethyluridine
4. 3',5'-Di-0-tert-butyldiphenylsilyl-5-monofluoromethyluridine

By following the procedure of Example 5 but using the corresponding acetylated nucleosides as the intermediates, the following nucleosides are also prepared in 10 % - 20 % yield.

1. 1-(3',5'-Di-0-acetyl-2'-chloro-2'-deoxy- β -D-arabinofuranosyl)-5-monofluoromethyluracil
2. 1-(3',5'-Di-0-acetyl-2'-bromo-2'-deoxy- β -D-arabinofuranosyl)-5-monofluoromethyluracil
3. 1-(2',3',5'-Tri-0-acetyl- β -D-arabinofuranosyl)-5-monofluoromethyluracil
4. 3',5'-Di-0-acetyl-2'-deoxy-5-monofluoromethyluridine
5. 3',5'-Di-0-acetyl-2'-deoxy-2'-fluoro-5-monofluoromethyluridine
6. 3',5'-Di-0-acetyl-2'-chloro-2'-deoxy-5-monofluoromethyluridine
7. 3',5'-Di-0-acetyl-2'-bromo-2'-deoxy-5-monofluoromethyluridine
8. 2',3',5'-Tri-0-acetyl-5-monofluoromethyluridine.

30 EXAMPLE 7

A solution of bromine (0.118 ml, 2.30 mmol) in carbon tetrachloride (2 ml) is slowly blown with a stream of dry nitrogen into a refluxing solution of 1-(5'-0-tert-butyldiphenylsilyl-2'-deoxy-2'-fluoro- β -D-arabinofuranosyl)thymine (498 mg, 1 mmol) in carbon tetrachloride while irradiated with a UV light. After 30 minutes, when

1 all the bromine is added, nitrogen is bubbled through the solution for a further 15 minutes to remove the hydrogen bromide.

5 The solution is concentrated to dryness in vacuo and the residue dissolved in dry acetonitrile (100 ml). Finely pulverized silver fluoride (1.0 g, 7.88 mmol), is added to the solution and the mixture is stirred vigorously for 15 minutes at room temperature. The mixture is

10 filtered and the filtrate is concentrated in vacuo. The residue is dissolved in chloroform, washed with water and saline, dried over sodium sulfate and concentrated in vacuo. The residue is chromatographed on a column of silica gel G60 using methylene chloride - tetrahydro-

15 furan (20:1 to 10:1) as the eluent. The UV absorbing fraction eluted with 10:1 methylene chloride - tetrahydrofuran is concentrated and the residue crystallized from methylene chloride - petroleum ether. 1-(5'-0-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro- β -D-arabinofuranosyl)-5-difluoromethyluracil (80 mg, 15 %) is obtained, mp 132-134°C. ^1H NMR (CDCl_3) & 1.08 (9H, s, tBu), 3.75-4.09 (3H, m, H-4', 5', 5''), 4.55 (1H, dq, H-3', $J = 22.23$, $J_{2',3'} = 0.82$, $J_{3',4'} = 0$ Hz), 5.05 (1H, dq, H-2', $J_{2',3'} = 51.05$, $J_{3',4'} = 3.30$, $J_{2',3'} = 0.82$), 6.77 (1H, dd, H-1', $J_{1',2'} = 19.49$, $J_{1',2'} = 3.30$) 6.56 (1H, t, CHF , $J_{\text{H},\text{F}} = 54.75$). 7.23-7.81 (10H, m, Ph), 7.87 (1H, d, H-6, $J_{\text{H},\text{F}} = 1.37$), 8.79 (1H, broad s, NH, exchangeable).

Microanalysis (C₂₆H₂₉F₃N₂O₅Si) Calcd: C, 58.41; H, 5.47; F, 10.66; N, 5.24. Found: C, 58.58; H, 5.69; F, 10.49; N, 5.19.

By following the same procedure but using the corresponding protected nucleosides, the following 5-difluoromethyluracil nucleosides are prepared:

- 1 1-(3',5'-Di-O-acetyl-2'-deoxy-β-D-erythropentofuranosyl)-5-difluoromethyluracil
- 1-(2',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-difluoromethyluracil
- 5 1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-arabinofuranosyl)-5-difluoromethyluracil
- 1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl)-5-difluoromethyluracil
- 1-(2',3',5'-Tri-O-acetyl-β-D-arabinofuranosyl)-5-difluoromethyluracil
- 10 1-(5'-0-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-β-D-arabinofuranosyl)-5-difluoromethyluracil
- 1-(5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl)-5-difluoromethyluracil
- 15 1-(2',5'-Di-O-tert-butyldiphenylsilyl-β-D-arabinofuranosyl)-5-difluoromethyluracil
- 1-(3',5'-Di-O-tert-butyldiphenylsilyl-β-D-arabinofuranosyl)-5-difluoromethyluracil
- 3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-5-difluoromethyluridine
- 20 3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-5-difluoromethyluridine
- 3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-5-difluoromethyluridine
- 25 2',3',5'-Tri-O-acetyl-5-difluoromethyluridine
- 5'-0-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-5-difluoromethyluridine
- 5'-0-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-5-difluoromethyluridine
- 30 5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5-difluoromethyluridine
- 2',5'Di-O-tert-butyldiphenylsilyl-5-difluoromethyluridine
- 3',5'Di-O-tert-butyldiphenylsilyl-5-difluoromethyluridine.
- 35

1 EXAMPLE 8

1-(5'-0-tert-Butyldiphenylsilyl-2'-deoxy- β -D-erythro-pentofuranosyl)-5-monofluoromethyluracil (440 ml, 0.88 mmol) is dissolved in dry tetrahydrofuran (4 ml) and 0.5 M tetra-n-butylammonium fluoride in tetrahydrofuran (2.2 ml) is added. The mixture is stirred at room temperature for 90 minutes and then concentrated in vacuo. The residue is chromatographed on a silica gel G60 column using methylene chloride-tetrahydrofuran (1:1) as the eluent. After concentration of the UV absorbing fraction, the residue is crystallized from acetone to give 2'-deoxy-5-monofluoromethyluridine, 143 mg (63 %), mp 140 °C (dec). ^1H NMR (d_6 -acetone) δ 2.21 (2H, m, H-¹⁵2',^{2"}), 3.71 (2H, m, H-¹⁵5',^{5"}), 3.88 (1H, apparent dd, H-¹⁵4', J_{3',4'} = 3.16, J_{4',5'} = 6.17, J_{5',5"} = 0 Hz), 4.39 (1H, m, H-3'), 4.96 (2H, d, CH₂F, J_{4',5"} = 49.12), 6.20 (1H, apparent t, H-1', J_{1',2'} = J_{1',2"} = 6.59, J_{2',2"} = 8.23 (1H, d H-6, J_{6,F} = 4.12).

20 Microanalysis (C₁₀H₁₃FN₂O₅) Calcd: C, 46.16; H, 5.03; F, 7.30; N, 10.76. Found: C, 46.28; H, 5.31; F, 7.16; N, 10.58.

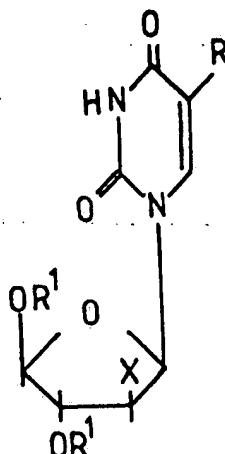
25 By following the same procedure but using the corresponding silylated nucleoside intermediates, the following 5-(partially fluorinated) methyluracil nucleosides are prepared:

30 1-(2'-Deoxy-2'-fluoro- β -D-arabinofuranosyl)-5-monofluoromethyluracil
 1-(2'-Chloro-2'-deoxy- β -D-arabinofuranosyl)-5-monofluoromethyluracil
 1-(2'-Bromo-2'-deoxy- β -D-arabinofuranosyl)-5-monofluoromethyluracil
 35 1-(β -D-arabinofuranosyl)-5-monofluoromethyluracil

- 1 2'-Deoxy-2'-fluoro-5-monofluoromethyluridine
- 2'-Chloro-2'-deoxy-5-monofluoromethyluridine
- 2'-Bromo-2'-deoxy-5-monofluoromethyluridine
- 5-Monofluoromethyluridine
- 5 1-(2'-Deoxy-2'-fluoro- β -D-arabinofuranosyl)-5-difluoromethyluracil
- 1-(2'-Chloro-2'-deoxy- β -D-arabinofuranosyl)-5-difluoromethyluracil
- 1-(2'-Bromo-2'-deoxy- β -D-arabinofuranosyl)-5-difluoromethyluracil
- 10 1-(β -D-Arabinofuranosyl)-5-difluorouracil
- 2'-Deoxy-5-difluoromethyluridine
- 5-Difluoromethyluridine
- 2'-Deoxy-2'-fluoro-5-difluoromethyluridine
- 15 2'-Chloro-2'-deoxy-5-difluoromethyluridine
- 2'-Bromo-2'-deoxy-5-difluoromethyluridine.

The results of antiviral assay of some representative nucleosides are given in Table I.

1 TABLE I.

Antiherpes Activity of α -fluorinated thymine nucleosides

15

Inhibitory Concentration (μ M) Toxic Concentration (μ M)

	R	R1	X	HSV-1	HSV-2	
20	CH_2F	H	H	>100	>100	1,000
	CH_2F	Ac	H	>100	>100	1,000
	CHF_2	H	H	1.40	1.66	1,000
	CHF_2	Ac	H	17.0	25.1	1,000
	CH_2F	H	F	0.21	0.18	1,000
	CH_2F	Ac	F	2.46	5.19	1,000
25	CHF_2	H	F	0.48	1.04	1,000
	CHF_2	Ac	F	0.71	2.16	1,000
	(FMAU) CH_3	H	F	0.10	0.05	1,000
	CH_3	Ac	F	0.44	1.23	1,000

30

35

- 1 Each of the nucleosides was initially dissolved in a diluent containing 60 % propylene glycol and 10 % EtOH; subsequent dilutions used maintenance culture medium.
- 5 Agents were assessed at tenfold dilutions with final concentrations ranging from 10,000 to 0.01 micromolar.

Confluent human foreskin monolayers were maintained in 96-well microtiter plates using Eagle's Minimal Essential Medium supplemented with 2 % fetal bovine serum, 10 antibiotics and glutamine using standard methods.

Prior to virus inoculation, the medium was removed from each well and replaced with 100 μ l of agent diluted in maintenance medium with differing concentrations in each horizontal row, beginning with the highest concentration 15 in the upper row, with subsequent tenfold dilutions in the next rows and the last (control) row fed with agent-free maintenance medium. The virus inocula were then added, suspended in 100 μ l of maintenance medium. A high-dose inoculum which induced nearly confluent (100 20 %) cytopathic effect (CPE) two days later was added to the first five vertical columns of the plate (1-5) and, similarly, a low-dose inoculum inducing approximately 50 % CPE in each well two days later was added to the next five vertical columns (6-10). To the last two columns, 25 virus-free medium was added to serve as uninfected control wells in order to assess direct cellular cytotoxicity at each agent dilution. The plates were then incubated at 36.9 $^{\circ}$ C in 9 % CO₂ in air for two days, at which time they were read.

30 The cytopathology of each well was read using an inverted microscope and scored from 0 to 4 (0 = no CPE and 4 = > 95 % CPE); for marginal or equivocal readings a + or - is affixed to each score. For calculation of the 35 inhibitory concentrations (IC) of agents and interpolating between dilutions of agents, each well reading was converted to a numerical score (4 = 40, 4- = 37, 3+ = 33;

1 3 = 30, etc). The mean score of each five wells in a row
Receiving a given agent dilution and virus inoculum was
then calculated and compared with an appropriate control
row receiving no agent. Significant inhibition was judged
5 to occur when the mean well score at a given agent
concentration was lower than the mean value of the
control row by 10 scoring units. When the value fell
between two rows, simple arithmetic interpolation was
done to calculate the agent concentrate at the point on
10 a slope between the mean scores in the rows above and
below this point. The IC values of each agent using the
high and low virus inocula were then averaged yielding a
final mean IC which was expressed as a micromolar drug
concentration.

15

Although α,α,α -trifluorothymidine (Formula IV, R = CF_3 ,
 $X = H$, $R^1 = H$) is reported to be antiherpetic and very
cytotoxic, the α,α -difluoro analog (Formula IV, R =
 CHF_2 , $X = H$ or AC , $R^1 = H$) showed very potent antiherpes
20 activity without serious cytotoxicity. In the FMAU series,
fluorination of the 5-methyl group does not alter
the antiherpetic activity significantly.

25 The acetylated derivatives may act as masked precursors
which may be saponified by esterases to release active
free nucleosides. The ^{18}F -labeled nucleosides which can
be prepared by the method we developed may be useful for
diagnosis of herpes encephalitis, employing Positron
Emission Tomography scanning.

30

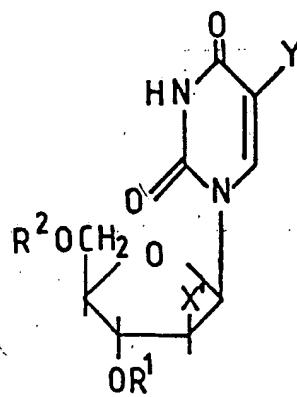
35

1 CLAIMS:

1. Pyrimidine nucleosides having the formula

5

10



wherein:

X or X' is H

15 X or X' is a halogen, pseudohalogen or OR³ wherein
³ R is H, acyl or trisubstituted-silyl;Y is CH₁F or CHF₂;20 R¹ and R² are the same or different and are H, acyl
 or trisubstituted-silyl.

25

2. Nucleosides of Claim 1 selected from the group of:

1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-
 arabinofuranosyl)thymine25 1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-
 arabinofuranosyl)thymine1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-
 arabinofuranosyl)thymine30 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-iodo-β-D-
 arabinofuranosyl)thymine1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-
 ribofuranosyl)thymine25 1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-
 ribofuranosyl)thymine1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-
 ribofuranosyl)thymine35 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-iodo-β-D-
 ribofuranosyl)thymine.

1 3. Nucleosides of Claim 1 selected from the group of:

5'-0-tert-Butyldiphenylsilylthymidine

1-(5'-0-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-
β-D-arabinofuranosyl)thymine

5 1-(5'-0-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-
β-D-arabinofuranosyl)thymine

1-(5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-
β-D-arabinofuranosyl)thymine

10 1-(2',5'-Di-0-tert-butyldiphenylsilyl-β-D-arabino-
furanosyl)thymine

1-(3',5'-Di-0-tert-butyldiphenylsilyl-β-D-arabino-
furanosyl)thymine

1-(5'-0-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-
β-D-ribofuranosyl)thymine

15 1-(5'-0-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-
β-D-ribofuranosyl)thymine

1-(5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-
β-D-ribofuranosyl)thymine

1-(2',5'-Di-0-tert-butyldiphenylsilyl-β-D-ribofura-
20 nosyl)thymine

1-(3',5'-Di-0-tert-butyldiphenylsilyl-β-D-ribofura-
nosyl)thymine.

4. Nucleosides of Claim 1 selected from the group of:

25 1-(3',5'-Di-0-acetyl-2'-deoxy-2'-fluoro-β-D-
arabinofuranosyl)-5-monofluoromethyluracil

1-(3',5'-Di-0-acetyl-2'-chloro-2'-deoxy-β-D-
arabinofuranosyl)-5-monofluoromethyluracil

1-(3',5'-Di-0-acetyl-2'-bromo-2'-deoxy-β-D-
30 arabinofuranosyl)-5-monofluoromethyluracil

1-(2',3',5'-Tri-0-acetyl-β-D-arabinofuranosyl)-5-
monofluoromethyluracil

3',5'-Di-0-acetyl-2'-deoxy-5-monofluoromethyluridine

3',5'-Di-0-acetyl-2'-deoxy-2'-fluoro-5-
35 monofluoromethyluridine

3',5'-Di-0-acetyl-2'-chloro-2'-deoxy-5-
monofluoromethyluridine

1 3',5'-Di-0-acetyl-2'-bromo-2'-deoxy-5'-
monofluoromethyluridine
2',3',5'-Tri-0-acetyl-5-monofluoromethyluridine.

5 5. Nucleosides of Claim 1 selected from the group of:
1-(5'-0-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-
β-D-arabinofuranosyl)-5-monofluoromethyluracil
1-(5'-0-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-
β-D-arabinofuranosyl)-5-monofluoromethyluracil
10 1-(5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-
β-D-arabinofuranosyl)-5-monofluoromethyluracil
1-(2',5'-Di-0-tert-butyldiphenylsilyl-β-D-
arabinofuranosyl)-5-monofluoromethyluracil
1-(3',5'-Di-0-tert-butyldiphenylsilyl-β-D-
arabinofuranosyl)-5-monofluoromethyluracil
15 5'-0-tert-Butyldiphenylsilyl-2'-deoxy-5'-
monofluoromethyluridine
5'-0-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-5'-
monofluoromethyluridine
20 5'-0-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-5'-
monofluoromethyluridine
5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5'-
monofluoromethyluridine
25 2',5'-Di-0-tert-butyldiphenylsilyl-5'-
monofluoromethyluridine
3',5'-Di-0-tert-butyldiphenylsilyl-5'-
monofluoromethyluridine.

30 6. Nucleosides of Claim 1 selected from the group of:
1-(3',5'-Di-0-acetyl-2'-deoxy-2'-fluoro-β-D-
arabinofuranosyl)-5-difluoromethyluracil
1-(3',5'-Di-0-acetyl-2'-chloro-2'-deoxy-β-D-
arabinofuranosyl)-5-difluoromethyluracil
1-(3',5'-Di-0-acetyl-2'-bromo-2'-deoxy-β-D-
arabinofuranosyl)-5-difluoromethyluracil
35 3',5'-Di-0-acetyl-2'-deoxy-5-difluoromethyluridine

1 3',5'-Di-0-acetyl-2'-deoxy-2'-fluoro-5-
difluoromethyluridine
3',5'-Di-0-acetyl-2'-chloro-2'-deoxy-5-
difluoromethyluridine
5 3',5'-Di-0-acetyl-2'-bromo-2'-deoxy-5-
difluoromethyluridine
2',3',5'-Tri-0-acetyl-5-difluoromethyluridine.

7. Nucleosides of Claim 1 selected from the group of:
10 1-(5'-0-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-
β-D-arabinofuranosyl)-5-difluoromethyluracil
1-(5'-0-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-
β-D-arabinofuranosyl)-5-difluoromethyluracil
1-(5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-
15 β-D-arabinofuranosyl)-5-difluoromethyluracil
1-(2',5'-Di-0-tert-butyldiphenylsilyl-β-D-
arabinofuranosyl)-5-difluoromethyluracil
1-(3',5'-Di-0-tert-butyldiphenylsilyl-β-D-
arabinofuranosyl)-5-difluoromethyluracil
20 5'-0-tert-Butyldiphenylsilyl-2'-deoxy-5-
difluoromethyluridine
5'-0-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-5-
difluoromethyluridine
5'-0-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-5-
25 difluoromethyluridine
5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5-
difluoromethyluridine
2',5'Di-0-tert-butyldiphenylsilyl-5-
difluoromethyluridine
30 3',5'Di-0-tert-butyldiphenylsilyl-5-
difluoromethyluridine.

8. Nucleosides of Claim 1 selected from the group of:
35 1-(2'-Deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-
monofluoromethyluracil
1-(2'-Chloro-2'-deoxy-β-D-arabinofuranosyl)-5-
monofluoromethyluracil

1 1-(2'-Bromo-2'-deoxy- β -D-arabinofuranosyl)-5-monofluoromethyluracil
1-(β -D-arabinofuranosyl)-5-monofluoromethyluridine
5-Monofluoromethyluridine
5 2'-Deoxy-5-monofluoromethyluridine
2'-Deoxy-2'-fluoro-5-monofluoromethyluridine
2'-Deoxy-2'-chloro-5-monofluoromethyluridine
2'-Deoxy-2'-bromo-5-monofluoromethyluridine.

10 9. Nucleosides of Claim 1 selected from the group of:

1-(2'-Deoxy-2'-fluoro- β -D-arabinofuranosyl)-5-difluoromethyluracil

1-(2'-Chloro-2'-deoxy- β -D-arabinofuranosyl)-5-difluoromethyluracil

15 1-(2'-Bromo-2'-deoxy- β -D-arabinofuranosyl)-5-difluoromethyluracil

1-(β -D-arabinofuranosyl)-5-difluoromethyluracil
5-Difluoromethyluridine

2'-Deoxy-5-difluoromethyluridine

20 2'-Deoxy-2'-fluoro-5-difluoromethyluridine

2'-Chloro-2'-deoxy-5-difluoromethyluridine

2'-Bromo-2'-deoxy-5-difluoromethyluridine.

10. Pharmaceutical composition comprising an effective
25 amount of nucleoside of formula defined in Claim 1.